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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,274	12/19/2001	David N. Herndon	D6197D	5877

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,274	HERNDON ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-4 and 17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group IX claims, claims 5-16, drawn to a gene therapy method of enhancing a wound healing in an external wound using a wound coverage/closure material impregnated with a cholesterol-containing cationic liposome having a gene encoding an insulin-like growth factor I, a thermal trauma species, and a human fetal amnion species, in the response filed September 16, 2003 is acknowledged.

Claims 1-4, 17-24 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

The cross-reference information on the fist paragraph of the specification must be amended to update the status of the parent '183 application.

The brief description of drawings is objected because the description of Figure 4, 12, or 13 does not contain any reference to Figures 4A, 4B, 12A, 12B, 13A and 13B, as depicted in the actual drawings. A change from "Figure 4 shows" to – Figures 4A-4B show --, and a change from "(4A)" to -- (Figure 4A) --, for example, would obviate the objection. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for:

A method of enhancing wound healing in an external wound of an individual, comprising the steps of :

Covering said wound with a wound coverage material, wherein said wound coverage material is impregnated with a therapeutically effective amount of a cholesterol-containing cationic liposome, said liposome comprising at least a gene construct encoding a growth factor.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The prior art of record and the specification provide sufficient guidance and/or evidence to reasonable enable one skilled in the art to practice the claimed invention directed to a method of enhancing wound healing in an external wound of a mammal, comprising the steps of :

Covering said wound with a wound coverage material, wherein said wound coverage material is impregnated with a therapeutically effective amount of a cholesterol-containing cationic liposome, said liposome comprising at least a gene construct encoding a growth factor. See Nakamura, Gene Therapy, Vol. 5, 1165-1170,

1995; US Pat No. 5,962,427; US Pat No. 4,361,552, US Pat No. 5,256,644, US Pat No. 6,132,765; US Pat No. 5,651,982, and US Pat No. 5,064,655, all of which are cited in the parent '183 application. Additional wound healing agents including wound dressings and/or wound coverage materials are also routinely employed in the art to treat an external wound of a mammal.

However, the currently pending claims do not *per se* require that a therapeutically effective amount of a cholesterol-containing cationic liposome, said liposome comprising at least a gene construct encoding a growth factor, is employed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The state of the art exemplified by Raz *et al.* (Vaccines, 94, pp. 71-75, 1994, cited in '183 parent application) indicates:

- "Under the conditions examined here, cationic lipid formulations (DMRIE-based formulation) did not improve the expression of the administered antigen gene as determined by measuring the corresponding antibody response" (page 73);

- "The results reported here indicate that cationic lipid DNA formulations can cause marked inflammation and tissue damage at the site of intradermal administration. The tissue damage and inflammation occur at a DNA concentration of 150 ug/ml and at cationic lipid/DNA ratios of 10 and 0.3" (page 74);
- "This vigorous inflammatory response may facilitate the clearance of the injected plasmid DNA and could lead to further tissue damage and spreading beyond the margins of the injection site. Thus, we believe that the tissue damage and the inflammatory response due by the cationic lipids in the dermis act in conjunction to diminish or event eliminate the transfective properties observed at the site of injection *in vivo"* (page 75);

Thus, it is apparent to a skilled artisan at the time of filing of this application that for any gene therapy method employing a cholesterol containing cationic liposomal vector comprising a DNA construct, an effective amount of the DNA construct in combination with the cationic liposomal vector must be carefully measured and is required for sufficient gene expression without causing toxicity and inhibiting gene expression. In fact, the as-filed specification states on page 25:

When used on a patient in therapy, the liposome vehicle described in the present invention is administered to the patient or an animal in therapeutically effective amounts, *i.e.,* amounts that effectively deliver appropriate amounts of the DNA encoding a growth enhancing agent.

In addition, the as-filed specification provides guidance and working examples showing that a therapeutically effective amount includes 10% liposomes or the highest concentration of a cholesterol- containing cationic liposome that could be employed in DNA transfer protocols without causing deleterious consequences on DNA solubility and is compatible with gene transfer paradigms, see Example 3.

As such, it is apparent that a skilled artisan could determines without any undue experimentation, as to what is appropriately considered as a therapeutically effective amount of a cholesterol containing cationic liposome/DNA construct for use within the context of applicant's invention, particularly in view of the totality of the prior art and guidance provided by the as-filed specification. Note also that the as-filed specification does not provide sufficient guidance as to what is exactly the effective weight and/or molar amount of DMRIE-C Reagent in the 10ul employed in the working examples. .

Thus, it is not apparent how one skilled in the art reasonably extrapolates from the basis of applicant's disclosure to the full scope of the claimed invention, without undue experimentation, particularly in view of the nature of the claimed invention, and the unpredictability factors regarding the nature of cationic liposomal vectors employed in an *in vivo* environment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6, 9, 11-13 are rejected under 35 U.S.C 103(a) are rejected under 35 U.S.C. 103 as being unpatentable over Goldstein *et al.* (US Pat No. 5,962,427) taken with McDonald *et al.* (US Pat No. 6,120,799).

Goldstein *et al.* in the '427 patent directed to a DNA gene therapy method for external wound healing by using a gene activated matrix containing DNA encoding a growth factor teaches that gene activated matrix material including implants, sponges, pads, wound dressings, sultures, dermal patches, cadaver skin are effective matrices for enhancing the migration of wound healing and/or repair cells from surrounding

tissues into a wound site that is covered by the matrices containing the therapeutic DNA (entire document, especially column 11, third paragraph, column 12, first paragraph, column 13, third paragraph, column17 bridging column 18, and column 24, last paragraph. A List of growth factors is disclosed on column 14, for example. Goldstein *et al.* does not teach the use of a cholesterol containing cationic as a carrier or vector for the growth factor encoded DNA, nor does Goldstein *et al.* teach explicitly the types of wound dressings or closure materials as recited in the Markush group of the claimed invention.

However, at the time the invention was made, McDonald *et al.* (column 2 bridging column 3, column 3 bridging column 4, columns 11, 16 and 17) teaches that a therapeutically effective amount of a cholesterol containing cationic liposome is routinely employed in the art as carriers of growth factor encoded DNA so as to enhance gene expression of the delivered DNA in target cells of an external wound, see column 3 bridging column 4, column 12, lines 10-65, column 16 bridging column 17, column 19, last full paragraph, column 20, last paragraph bridging column 21.

It would have been obvious for one of ordinary skill in the art to have employed cholesterol-containing cationic liposomes as carriers or vectors of the DNA of Goldstein *et al.* so as to enhance the wound healing process of an external wound (bone rupture, ligament wound, thermal wound, or external wounds as a result of any trauma known in the prior art) in an individual. One of ordinary skill in the art would have been motivated to have employed the liposomes employed in the cited references because McDonald

et al. is one of many prior art of record, which teaches that cholesterol-containing cationic liposomes are routinely employed in the art as effective carriers of therapeutic materials or wound enhancing growth factor encoding gene construct to enhance an efficacy of gene expression of the gene construct at its target site.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 5, 9, 11, and 15 are rejected under 35 U.S.C 103(a) are rejected under 35 U.S.C. 103 as being unpatentable over Goldstein *et al.* (US Pat No. 5,962,427) taken with McDonald *et al.* (US Pat No. 6,120,799), and further in view of Coleman (US 2003/0018984).

Goldstein *et al.* taken with McDonald *et al.* are applied here as indicated above. Goldstein *et al.* taken with McDonald *et al.* do not teach explicitly that a growth factor is IGF-I.

However, at the time the invention was made, Coleman teaches that IGF-I encoding expression vector is effective for use to treat an external wound as a result of a nerve crush, see par. 0007, page 1, and par. 0314, page 27. Cationic liposome used as a DNA carrier is also disclosed on par. 0264 of page 23.

It would also have been obvious for one of ordinary skill in the art to employ an IGF-I encoding gene construct in the wound coverage material of Goldstein *et al.* taken with McDonald *et al.* One of ordinary skill in the art would have been motivated to employ an IGF-I as a growth factor gene in the wound dressings and/or wound closure materials as wound healing agents because of the advantages as disclosed in

Goldstein taken with McDonald, and because Coleman teaches that IGF-I expressing vector can be used to enhance a muscle healing in damage nerve tissues in an external wound such as a nerve crush.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 5-8, 11-14 are rejected under 35 U.S.C 103(a) are rejected under 35 U.S.C. 103 as being unpatentable over Goldstein *et al.* (US Pat No. 5,962,427) taken with McDonald *et al.* (US Pat No. 6,120,799), and further in view of anyone of Baur (US Pat No. 4,361,552), Boyce (US Pat No. 5,976,878), Kushner (US Pat No. 5,741,509), and applicant's admission over the prior art on page 29 of the specification.

Goldstein *et al.* taken with McDonald *et al.* are applied here as indicated above. Goldstein *et al.* taken with McDonald *et al.* do not teach explicitly the types of wound dressings or closure materials as recited in the Markush group of the claimed invention, human fetal aminion.

However, Baur, Boyce, Kushner, and applicant 's admission over the prior art are exemplified references which teach that it is routine in the art at the time the invention was made for one of ordinary skill in the art to have employed wound dressing materials and/or wound closure materials including human fetal amnion on an external wound of an individual so as to enhance the wound healing of the wound.

It would also have been obvious for one of ordinary skill in the art to have further incorporated the liposomal composition of the combined cited references in a wound dressings and/or wound closure material as described in the cited references in order to

enhance the wound healing process in any individual having an external wound. One of ordinary skill in the art would have been motivated to have employed the wound dressings and/or wound closure materials as wound healing agents because of the advantages as disclosed in Goldstein, Baur, Boyce, and, Kushner, and because Goldstein teaches that as long as a gene activated matrix is employed together with a DNA construct encoding a growth factor on an external wound of an individual, an enhancement of wound healing processes can be generated. One of ordinary skill in the art would have a reasons expectation of success to practice the claimed invention particularly in view of the working examples and/or disclosures of the combined cited references, and given the state of the art as a whole, as exemplified by the combined cited references.

Thus, the claimed invention as a whole was *prima facie* obvious.

To the extent that the claimed invention is directed to a method of enhancing wound healing in an external wound of an individual, comprising the steps of :

Covering said wound with a wound coverage material, wherein said wound coverage material is impregnated with a therapeutically effective amount of a cholesterol-containing cationic liposome, said liposome comprising at least a gene construct encoding an insulin-like growth factor-I (IGF-I), and wherein the concentration of said at least one gene is about 2.2 ug/10 ul liposomes (claims 10, 16), the claimed invention is free of the prior art, particularly in view of the data shown on page 59 of the

specification. However, the elected and enabling claimed embodiment is subjected to the following obviousness double patenting rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No 6,576,618 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are drawn to a wound coverage material, wherein said wound coverage material is impregnated with a therapeutically effective amount of a cholesterol-containing cationic liposome, said liposome comprising at least a gene construct encoding an insulin-like growth factor-I (IGF-I), and

wherein the intended use of the wound coverage material is employed to enhance wound healing in an external wound.

Thus, both sets of claims are obvious variants of one another.

No claims are allowed.

The references, which are cited in the parent '892 case, will not be provided herein unless requested by applicants.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0184.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER